subject matter. Applicants reserve the right to pursue the subject matter of the cancelled claims in related applications. Claims 24-88, 102-131, 141-205, and 219-247 are currently pending. Claims 35, 76, 102, and 219 have been amended to correct minor editorial and/or typographical errors. The claims are completely supported in the specification and no new matter has been introduced.

Formal Matters/Amendments

Claims 35, 76 and 102 were objected to due to informalities. This objection has been obviated by amendment of these claims to correct these informalities.

Claims 93-95 and 210-212 were objected to under 37 CFR 1.75(c) for being in improper dependent form because they failed to further limit the subject matter of a previous claim. Claims 210-212 have been cancelled, thus obviating this rejection of these claims. Further, Applicants disagree and assert that claims 93-95 do further limit the subject matter of the claim from which they depend. For example, claim 90 claims N-terminal deletion of up to 48 amino acid residues (i.e., a range between 1 and 48 amino acid residues) of the polypeptide encoded by the cDNA clone contained in ATCC Deposit No. 97810. Claim 93, which depends from claim 90 claims an N-terminal deletion of 48 amino acid residues (i.e., a point in the range of claim 90) of the polypeptide encoded by the cDNA clone contained in ATCC Deposit No. 97810. Thus, claim 93 specifies a further limitation of the subject matter of claim 90. Similar arguments can be made for each of claims 92 and 93. Therefore, Applicants respectfully request that this objection be withdrawn.

The Claimed Invention is Adequately Enabled under 35 USC §112, First Paragraph

The Examiner rejects claims 46-75 and 141-192 under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable one of skill in the art to make and/or use a polypeptide sequence comprising the amino acid sequence of SEQ ID NO:4 or a polypeptide comprising an amino acid sequences 90% or 95% identical to SEQ ID NO:2 or 4 commensurate in scope with the claims.

The Examiner acknowledges that the specification adequately enables the use of the TNFR-6alpha polypeptide shown in SEQ ID NO:2. However, the Examiner asserts that because of sequence difference between the polypeptide encoded by SEQ ID NO:2 and that

of SEQ ID NO:4 , or polypeptides 90 or 95% identical to SEQ ID NOS: 2 or 4 make it difficult to predict the function of these polypeptides and that the "Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine without undue experimentation, the positions in the protein which are tolerant to change (e.g., such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions."(*See,* Paper 14, Page 5, lines 14-19).

Applicants respectfully disagree and traverse.

Preliminarily, Applicants point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to make the claimed polypeptides and practice a single use thereof without undue experimentation.[1] Thus, Applicants submit that to be fully enabled, the polypeptides of the invention need merely have application in a single use, such as, to mediate a cellular response (e.g., modulating cell proliferation, for example, by inhibiting apoptosis) in response to binding to a TNF family ligand such as FasL, or to generate a TNFR-6alpha and/or TNFR-6beta specific antibody.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

Furthermore, "[t]here is no magical relation between the number of representative examples and the breadth of the claims" with respect to enablement. *In re Borkowski*, 164 USPQ 642, 646 (C.C.P.A. 1970). The issue is not whether the specification discloses any or all alterations that can be made in the claimed polypeptides that will not alter the functional

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1 The Applicant need show utility for only one disclosed purpose. See *Raytheon Co. v. Roper Corp.*, 220 USPQ 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 USPQ 223 (Pat. Off. Bd. App. 1958).

activity of the polypeptides, but rather whether polypeptides encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art. See *In re Angstadt*, 190 USPQ 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . .

While the predictability of the *art* can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the *result* of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). Since the disclosed or otherwise known methods of making and screening polypeptides (and fragments or variants thereof) may be used to make and then *determine*, without undue experimentation, whether a given TNFR polypeptide encompassed by the claims is able to mediate a cellular response (e.g., modulating cell proliferation, for example, by inhibiting apoptosis) in response to binding to a TNF family ligand such as FasL

or to generate a TNFR-6alpha and/or TNFR-6beta specific antibody, and therefore possesses the disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989).

Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make and use the claimed polypeptides of the present invention. For example, the specification discloses both the nucleic acid and amino acid sequences of TNFR-6alpha (SEQ ID NOS: 1 and 2, respectively) and TNFR-6beta (SEQ ID NOS: 3 and 4, respectively), routine molecular biology techniques for generating polynucleotide and polypeptide variants (*see, e.g.*, pp 40-41 which disclose methods of producing TNFR variants, pp. 49-62 which disclose routine cloning methods), TNFR activity (*see, e.g.*, page 23, lines 8-23) and biological assays including for example, assays to determine if a polypeptide mediates a cellular response in response to binding to a TNF family ligand such as FasL (see page 47, line 12 to page page 48, line 16, page 25, line 1 to page 26, line 8 and Examples 7, 8, and 9).

Applicants disagree with the Examiner's assertion that the "Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine without undue experimentation, the positions in the protein which are tolerant to change (e.g., such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions."(*See,* Paper 14, Page 5, lines 14-19). In particular, Applicants would like to bring the disclosure of page 97 to the Examiner's attention as it provides specific guidance for making phenotypically silent amino acid substitutions in a polypeptide, thus guiding the skilled artisan as to which TNFR-6alpha and/or TNFR-6beta polypeptide variants are likely to retain TNFR activity. Further, the specification identifies TNFR-6alpha and TNFR-6beta as a members of the Tumor Necrosis Factor Receptor Family based on its homology to other Tumor Necrosis Factor Receptors and identifies regions conserved (i.e., the conserved cysteine rich domains) among members of this protein family (*see, e.g.*, page 5, lines 20-24, Page 13, lines 13-22, and Figure 3 of the instant specification). Using the provided alignment, the skilled artisan could therefore identify regions of TNFR-6alpha and/or TNFR-6beta which could tolerate alterations based on the homology shared between TNFR-6alpha and/or TNFR-6beta and other Tumor Necrosis Factor Receptor Family members.

Moreover, the skill in the art of molecular biology is high. Applicants submit that the skilled molecular biologist, enlightened by the teaching of the present specification and armed with the knowledge available in the art at the time of filing of the captioned application, would be more than capable of routinely making proteins with at least 90% or 95% sequence identity with the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 or with the polypeptide encoded by the cDNA in ATCC Deposit Nos. 97810 or 97809 that display TNFR activity. In addition, the instant specification teaches for example, assays which could be used to measure the ability of a TNFR-6alpha and or TNFR-6beta polypeptide of the invention to inhibit Fas Ligand induced apoptosis. Armed with this disclosure, the skilled artisan could readily and routinely test whether a protein with at least 90% or 95% sequence identity with the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 or with the polypeptide encoded by the cDNA in ATCC Deposit Nos. 97810 or 97809 has such activity.

The claimed polypeptides are enabled for the reasons put forth above, and furthermore, the claimed polypeptides are enabled for purposes unrelated to their biologic activity. Applicants again point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, first paragraph, the specification need only enable a person of ordinary skill in the art to make the claimed polypeptides and practice a single use of the claimed polypeptides without undue experimentation.[2] Thus, Applicants submit that to be fully enabled, the claimed polypeptides need merely have application in a single use, such as, for example, to bind an antibody to a protein of the invention, or to function antagonistically to a TNFR protein of the invention. Applicants submit that, in the present case, it would not require undue experimentation on the part of one of ordinary skill in the art to make and use polypeptides having at least 90% or 95% sequence identity with the amino acids of SEQ ID NO:2 or SEQ ID NO:4 or with the polypeptide encoded by the cDNA in ATCC Deposit Nos. 97810 or 97809. For example, polypeptides having at least 90% or 95% sequence identity with the amino acids of SEQ ID NO:2 or SEQ ID NO:4 or with the polypeptide encoded by the cDNA in ATCC Deposit Nos. 97810 or 97809 would be useful in routinely generating antibodies against TNFR polypeptides as disclosed in the "Antibodies" section of the instant

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[2] The Applicant need show utility for only one disclosed purpose. See *Raytheon Co. v. Roper Corp.*, 724 F. 2d 951, 220 U.S.P.Q. 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 U.S.P.Q. 223 (Pat. Off. Bd. App. 1958).

specification (pages 109-154, and in particular, pages 114-120). It is noted that it was well known in the art on the priority date of the present application that antibodies can be made to polypeptides (and fragments or variants thereof) even though they may not be immunogenic in an animal using methods such as phage display.

Applicants submit that because the disclosed or otherwise known methods of making and screening polypeptides (and fragments or variants thereof) may be used to make and then *determine*, without undue experimentation, whether a given polypeptide (or fragment or variant thereof) encompassed by the claims is able to mediate a cellular response in response to binding to a TNF family ligand or to generate a TNFR-6alpha and/or TNFR-6beta specific antibody, and therefore possesses the disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989).

A patent Applicant's specification disclosure which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d. 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). Applicants submit that the Examiner has provided no evidence to doubt the enablement of the claimed TNFR6-alpha and or TNFR6-beta polypeptides of the invention.

In view of the foregoing, Applicants submit that the claims fully meet the enablement requirements of Section 112, first paragraph, and respectfully request that the rejection be withdrawn.

Availability of Deposited Plasmids

The Examiner rejected claims 35-45, 61-75, 89-101, 117-123, 152-162, 178-192, and 206-218 under 35 USC §112, first paragraph as not being enabled because enablement of these claims allegedly requires availability of the specific plasmids (ATCC Deposit Numbers 97810 and 97809) claimed therein.

The undersigned attorney of record in the instant application hereby states that, except for the limitations allowed by 37 C.F.R. § 1.808(b), the deposited plasmid HPHAE52, accorded ATCC Deposit Number 97810, will be irrevocably and without restriction released to the public upon the issuance of a patent containing claims reciting said plasmid for the instant application.

The undersigned attorney of record in the instant application hereby states that, except for the limitations allowed by 37 C.F.R. § 1.808(b), the deposited plasmid HTPCH84, accorded ATCC Deposit Number 97809, will be irrevocably and without restriction released to the public upon the issuance of a patent containing claims reciting said plasmid for the instant application.

Applicants believe that all the requirements of 37 C.F.R. §§ 1.801-809 have been met with respect to the deposited plasmids. Therefore, Applicants respectfully request that the rejection under 35 USC §112, first paragraph be withdrawn.

The Claimed Invention is Definite under 35 USC §112, Second Paragraph

Claims 219-232 are rejected under 35 USC §112, second paragraph as being indefinite because claim 219 did not contain sections (c), (d), (e), (f), and (g) which are referred to in the dependent claims. This rejection is obviated by the amendment to claim 219.

The Claimed Invention is Novel under 35 USC §102(e)

Claims 24-29, 31, 33, 35-40, 42, 44, 46-55, 57, 59, 61-70, 72, 74, 76-83, 85, 87, 89-96, 98, 100, 102-111, 113, 115, 117, 118, 120, 122, 124-126, 128, 130, 206, 208, 209, 211-213, 215, 217, 219-224, 226, 227, 229, 231, 233, 234, 236, 238, 240-242, and 246 have been rejected under 35 U.S.C. §102(e) as being anticipated by Emery et al., U.S. Patent Number 5,885,800 filed February 4, 1997 and granted March 23, 1999. This rejection is obviated by the fact that the instant application has an effective filing date of January 14, 1997, 21 which is prior to the February 4, 1997 filing date of the Emery et al. reference. The instant application is a continuation-in-part of U.S. non-provisional application serial No. 09/006,352, filed 13 January, 1998, which in turn, claims the benefit of priority to U.S. Provisional Application Serial No. 60/035,496, filed January 14, 1997. Applicants have amended the specification to correctly identify all the applications to which the instant application claims priority. Applicants respectfully request that the rejection under §102(e) be withdrawn.

The Claimed Invention is Novel under 35 USC §103(a)

Claims 32, 43, 73, 86, 99, 114, 121, 129, 216, 230, 237, and 245 have been rejected under 35 U.S.C. §103(a) for alleged obviousness over Emery et al., U.S. Patent Number 5,885,800 filed February 4, 1997 and granted March 23, 1999 in view of U.S. Patent Number 4, 847,325 to Shadle et al., granted on July 11, 1989. Further claims 30, 34, 41, 45, 56, 60, 71, 75, 84, 88, 97, 101, 112, 116, 119, 121, 123, 127, 131, 214, 218, 228, 232, 235, 239, 243, and 247 have been rejected under 35 U.S.C. §103(a) for alleged obviousness over Emery et al., U.S. Patent Number 5,885,800 filed February 4, 1997 and granted March 23, 1999 in view of U.S. Patent Number 5,985,614 to Rosen et al., granted on November 16, 1999. As detailed above, Emery et al. is not available as prior art under 35 U.S.C. §102(e). Neither Shadle et al. or Rosen et al, teach or suggest the claimed compositions. Thus, the claimed subject matter is not obvious in view of the cited references. Accordingly, Applicants respectfully request that the rejection under §103(a) be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks above be entered and made of record in the file history of the instant application. Should any additional fees be deemed necessary, please charge such fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: MAY 4, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Gentz et al.

Application Serial No.: 09/518,931 Art Unit: 1632

Filed: March 3, 2000 Examiner: TBA

For: Tumor Necrosis Factor Receptors 6alpha & 6beta Attorney Docket No.: PF454P1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in bold with insertions indicated with underlining and deletions indicated by strikeout.

In the Specification:

The first paragraph of the application beginning on line 3 of page 1, has been amended as follows:

This application is a continuation-in-part of application serial No. 09/006,352, filed 13 January, 1998, ~~**which is herein incorporated by reference in its entirety,**~~ priority to which is hereby claimed under 35 U.S.C. §120. **Application Serial No. 09/006,352, in turn, claims the benefit of priority under 35 U.S.C. §119(e) based on U.S. Provisional Application Serial No. 60/035,496, filed January 14, 1997.** ~~**In addition, priority of the following provisional applications is hereby claimed**~~ **This application also claims the benefit of priority** under 35 U.S.C. §119(e) **based on the following U.S. Provisional Applications**: Serial No. 60/121,774, filed 04 March 1999, Serial No. 60/124,092, filed 12 March 1999, Serial No. 60/131,279, filed 27 April 1999, Serial No. 60/131,964, filed 30 April 1999, Serial No. 60/146,371, filed 02 August 1999, and Serial No. 60/168,235, filed 01 December 1999~~**, each of which**~~**.** **Each of the above referenced applications** is hereby incorporated by reference in its entirety.

In the Claims:

Claim 35 has been amended as follows:

35. (Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of the full-length polypeptide encoded by the cDNA clone contained in ATCC Deposit No. 97810;

(b) the amino acid sequence of the full-length polypeptide excluding the N-terminal methionine residue encoded by the cDNA clone contained in ATCC Deposit No. 97810;

(c) the amino acid sequence of the mature polypeptide encoded by the cDNA clone contained in ATCC Deposit No. 97810; and

(d) the amino acid sequence of the extracellular domain of the polypeptide ~~is~~ encoded by the cDNA clone contained in ATCC Deposit No. 97810.

Claim 76 has been amended as follows:

76. (Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acid residues m-300 of SEQ ID NO:2, where m is an integer from 1 to 49;

(b) amino acid residues 1-y of SEQ ID NO:2, where y is an integer from 193-300; and

(c) amino acid residues m-y of SEQ ID NO:2, where m is an integer from 1 to 49 and where y is an integer from 193-300~~;~~.

Claim 102 has been amended as follows:

102. (Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acid residues 31 to 46 of SEQ ID NO:2;

(b) amino acid residues 57 to 117 of SEQ ID NO:2;

(c) amino acid residues 132 to 175 of SEQ ID NO:2;

(d) amino acid residues 185 to 194 of SEQ ID NO:2;

(e) amino acid residues 205 to 217 of SEQ ID NO:2;

(f) amino acid residues 239 to 264 of SEQ ID NO:2;

(g) amino acid residues 283 to 298 of SEQ ID NO:2; and

(h) an epitope bearing fragment of amino acid residues 1 to 300 of SEQ ID NO:2.

219. (Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acid residues 31 to 46 of SEQ ID NO:4;

(b) amino acid residues 57 to 80 of SEQ ID NO:4;

~~(i)~~ **(c)** amino acid residues 86 to 106 of SEQ ID NO:4;

~~(j)~~ **(d)** amino acid residues 108 to 119 of SEQ ID NO:4;

~~(k)~~ **(e)** amino acid residues 129 to 138 of SEQ ID NO:4;

~~(l)~~ **(f)** amino acid residues 142 to 166 of SEQ ID NO:4; and

an epitope-bearing fragment of amino acid residues 1 to 170 of SEQ ID NO:4.